

Bayer 9265.2-KGB
Le A 30 349-US-02 Rt/HB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS : HUBERT DORN ET AL.
SERIAL NO. : 08/925,372
FILED : September 8, 1997
FOR : NON-SYSTEMIC CONTROL OF PARASITES
ART UNIT : 1616
EXAMINER : A. Robinson.

8/5/99

28
SUCPP
8-10-99

August 4, 1999

Hon. Assistant Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

SIR:

In accordance with 37 CFR §§1.56, 1.97(b), and 1.98, Applicants wish to call the attention of the Examiner to the references listed on the attached Form PTOL-1449. Copies of each of the cited references is attached.

Since this information disclosure statement is being filed before the first Office Action on Applicants' request for this continued prosecution application, Applicants believe that no fee is due for consideration of this information disclosure statement. However, should the Assistant Commissioner determine that a fee is, in fact, due, he is hereby authorized to charge such fee to Deposit Account No. 02-1445.

Before discussing the relevance of each of the cited references, Applicants wish to point out that these references were cited by Novartis Corporation in connection with an opposition filed by Novartis against the corresponding Australian patent application. Copies of the opposition papers are attached in addition to the cited references.

Turning to the references individually:

1. EP-A 590 425 (Reference D1).

The reference shows that the active compounds used according to the present invention had been known before the filing date in Australia and before the German priority date. The instant application claims a specific use of these compounds but not the compounds themselves. Therefore, the reference is totally irrelevant with respect to the present invention.

The reference discloses the use of the active compounds, which are used according to the present invention, against fish parasites. A person skilled in the art with the task to find a dermal treatment of a warm-blooded animal like a dog would not even look for the solution of his problem at a reference describing treatment of fish. This is especially true if the treatment method according to the present

invention is considered. The reference discloses on page 7, lines 43 ff, oral treatments and on page 7, lines 47, treatment of the surrounding of the treated animal. With oral treatment, one achieves exactly what is not wanted here, that is the systemic use. With treatment of the surrounding, one achieves a treatment method which is easily used in the case of fish but which is not favored when used on cats and dogs. In case of fish treatment the treatment via the surroundings means the active compound is automatically and continuously brought onto the surface of the parasite. This treatment would be comparable in agricultural plant protection with the treatment of e.g. aphids sitting on plants by spraying plant and parasites completely. But even this is not true analogy because with spraying the parasite is only in contact with the treatment medium during the short moment of spraying. It could well be argued that the plant parasite takes up most of the active compound systemically that is by sucking the plant saps which contain the active compound. In other words this reference gives no clue that dermal treatment of warm-blooded animals with compounds of formula I could be used to free them from parasites located on their surface.

2. Brighton Corp Protection Conference Tests and Diseases No. 1, 1990 p. 21-18 Elbert et al. (Reference D2)

The reference describes the agrochemical use of Imidacloprid. This means the active compound is used in the form of formulations adapted to its use on plants,

seeds or in soil against plant damaging insects. The insects listed in the Abstract of the reference are such plant damaging insects. (They are neither identical nor from their taxonomic order related to fleas.) This means the reference discloses pests and treated subjects different from those of the present invention. For those skilled in the art it is not reasonable to automatically draw conclusions from the activity of a chemical against plant damaging insects to its suitability against parasites on animals. Also the fact that the compound described in the reference has low mammalian toxicity does not make it automatically suitable to combat fleas on dogs and cats by dermal application.

The reference specifically mentions the excellent systemic activity of Imidacloprid. This means it was known that the active compound is taken up into the sap-streams of the plant, it is distributed by the sap-stream within the plant and then taken up orally by the plant-parasite sucking the plant-sap. If anything this reference clearly would lead away from the present invention because it indicates that the active compound has to be taken up orally and this means it teaches the direct opposite to the present invention, that is the systemic use.

3. Pap. Intl. Congr. Pest-Chem. 1978, Publ. 1979, 449-457 Jones et al. (Reference D3)

This reference describes the mode of action of certain insecticides. These

insecticides interact with the acetylcholine receptor of insects. The reference neither discloses the use of compounds of present formula I against insects, nor discloses any methods of use of these compounds, nor discloses the dermal use of these compounds against fleas on dogs and cats. The reference takes for granted that active compounds are transported to their location of action. The reference gives no indication in which way the compounds are applied and how they are transported to their location of action.

The reference does not give a practical solution to the problem how the active compound is applied to a treated animal nor does it solve the problem how the active compound is taken up by the parasite, nor does indicate how it is brought to the receptor where it acts.

4. WO 93/24 002 (Reference D4)

This reference is cited on page 1 of the specification of the present patent. The present invention is clearly distinguished from this reference by claiming non-systemic use. In contrast thereto the reference claims and describes the advantage of systemic use of certain compounds. The reference does so by distinguishing the claimed systemic method from known dermal methods. According to this reference, these dermal methods are disadvantageous. For

instance on page 6, lines 10-34, it is stated that spot-on formulations containing some organophosphorus compounds generally have good short-term activity only. The reference sees clear disadvantages in the dermal treatment and therefore distinguishes the claimed systemic use from these known methods.

In the present invention, the inventors take up this dermal treatment disregarded by reference D-4 and demonstrate that it not only works excellently but that is also allows the long-term activity the reference is missing. What Applicants found is that with the dermal method discredited by the reference they even get longer activity than with the highly praised systemic treatment method.

5. US-P 4 741 060 (Reference D5)

This reference discloses new active compounds and among others Imidacloprid. The reference also discloses that these active compounds can be used as insecticides. In column 52 lines 45-56 the reference indicates that the new active compounds may be used in the field of veterinary medicine against noxious animal parasites (endo- and ecto-parasites) such as insects and worms. The reference is silent about the treatment method. The reference does not distinguish between systemic and non-systemic treatment methods. Endo-parasites (worms) necessarily have to be combated by a method which brings active compound into the treated

nimal - this would be a systemic treatment. Ecto-parasites would be treated in principle systemically and nonsystemically. But as reference D4 (published December 9, 1993) so convincingly points out also in the case of ecto-parasites in the animal health field systemic treatment is the most advantageous method.

Therefore D5 and D4 taken together clearly lead away from the treatment method according to the present invention.

6. EP-A 376 279 (Takeda) (Reference D6)

The reference discloses insecticidally active compounds. The reference discloses that these active compounds can be used in the agricultural horticultural and/or home-gardening field (page 2, lines 31-32). At page 7 lines 43-33 it is mentioned that the compounds can be used as insecticides in any application form suited generally for agricultural chemicals. At page 8, lines 31-33 it is mentioned that the compounds can exert potent insecticidal activities when they are directly contacted with insects e.g. by applying to their living animals or plants. No indication is given how this "contact" is achieved in case of treatment of animals. Again reference D4 here gives a good evaluation of the treatment methods and their advantages and disadvantages. Therefore also reference D6 together with reference D4 would lead the man skilled in the art to use the compounds of D6 in the

preferred systemic use method disclosed in D4.

7. EP-A 302 833 (Ciba) (Reference D7)

The reference discloses insecticidally active new compounds. On page 7, lines 29-30 it is mentioned that the compounds are useful to control pests on animals and plants. At lines 40-42 as pests to be controlled on animals ectoparasites e.g. mites, ticks and diptera like *lucila sericata* are mentioned. With respect to the application method it is simply mentioned on page 7, lines 49-51, that the active compounds are chosen in accordance with the intended objectives and prevailing circumstances. In other words the reference is completely silent with respect to the most essential part of the present invention. In other words the addressee of this reference is left in this respect with this general knowledge or with prior art. The closest prior art for this use was D-4. Therefore, also D7 has to be seen together with D4 and therefore does not anticipate or make obvious the present invention.

8. EP-A 306 696 (Ciba) (Reference D8)

As with references D6 and D7 reference D8 discloses insecticidally active compounds. Also this reference mentions that the active compounds can be used to control pests that attack plants and animals. But again the reference is silent as to

the specific method which is to be used advantageously to apply these compounds. A passage cited by Novartis during the opposition from col. 4, lines 28-39 of the US-Pat. is not completely cited. The citation in the original EP-A 306 696 refers to sucking insects of the family aphididae (like e.g. *aphis fabae*, *aphis craccivora* and *myzus persicae*) which are difficult to be combated by usual compositions. This passage therefore clearly refers to plant damaging pests and to application methods against plant damaging pests. No conclusion can be drawn from this passage to any application method useful against animal parasites. On Col. 4, lines 64-68, which refers to control of ectoparasites nothing is said about any suitable application method. Therefore also this reference is totally silent with respect to one of the most essential parts of the present invention.

Even example 5 which should demonstrate activity against *lucilia sericata* - a fly molesting animals - simply shows that the freshly hatched adults are damaged when in contact with a nutrient treated with the active compound. The example says nothing about any treatment method of an animal to be protected from the pest.

Also here reference has to be made to the most suitable application method on animals as disclosed in D-4.

9. EP-A 471 372 (Takeda) (Reference D9)

Also this reference discloses new insecticidally active compounds. The reference makes general remarks as to the application methods. At page 15 lines 6-9 it is mentioned that the compounds "are effective in controlling sanitary or horticultural insect pests and animal/plant parasitic insects and exhibit potent insecticidal action when contacted directly with insects, for example, by being sprinkled directly over animals and plants with insect pests parasitic thereon". Obviously this citation refers to an application method principally useful for both animals and plants. Such a method could be the spray method. But also here D4 fully describes the disadvantages of this method when used on animals. Therefore the man skilled in the art would take this passage from reference D9 for what it is, an exemplification for all imaginable possibilities. Such person would not consider this as a particularly useful method, or a description of the present invention.

10. EP-A 364 844 (NBA) (Reference D10)

Also this reference discloses primarily new insecticidally active compounds. A page 8, lines 15, to page 9, line 10, all sorts of pests are mentioned without discrimination to agriculture, forestry, stored product protection, hygiene. At page 9, lines 11-16, general activity against animal parasitic pests is mentioned. No specific

application is mentioned for these compounds in the field of use on animals. Therefore the argumentation advanced above against references D6-D8 is also applicable here.

11. EP-A 493 369 (Takeda) (Reference D11)

The reference discloses insecticidally active compounds. The disclosure with respect to their use and their application methods is almost identical with that in reference D6. Therefore the argumentation advanced above against reference D6 fully applies also here.

12. EP-A 381 130 (Takeda) (Reference D12)

The reference discloses insecticidally active compounds. The disclosure with respect to their use and their application methods is almost identical with that in reference D6. Therefore the argumentation advanced above against reference D6 fully applies also here.

13. EP-A 529 680 (Takeda) (Reference D13)

Novartis particularly highlights in this reference the passage bridging page 17

and 18 where it is stated that the compounds "are effective in the control of household pests and animal or plant parasitizing insects and mites, and exhibit strong pesticidal effects as a contact poison when applied directly to the host animals and plants". Nothing is mentioned how the compounds are applied directly to the host animal, but the reference continues on page 18, lines 2-6: "The most salient feature of the compound, however, is that it displays potent pesticidal effects even after it has been absorbed into plants via the root, leaf, stem or the like and come into contact with the pests as the pests suck or gnaw on the plants. This property is advantage in the control of sucking/biting insects and ticks." This citation clearly means that at least on plants systemic action and application methods based thereon are considered by this reference as most suitable. Together with the disclosure of reference D4 which clearly points out the disadvantages of contact based application methods on animals this remark would lead away the skilled worker to consider a contact based method for animals. The more so as such method only is implicitly mentioned for animals in this reference, but not specifically recommended.

14. EP-A 302 389 (Takeda) (Reference D14)

As the wording for use and application methods in this reference is almost identical as in reference D13, the same argumentation above against D13 applies here.

15. US-P 5 302 605 (Ciba) (Reference D15)

The reference discloses insecticidally active components. As in the many cases above the reference indicates in the form of general remarks that the compounds can be used against all sorts of pests and among others to " ... insects that are harmful to domestic animals and productive livestock". Nothing is said about application methods specifically adapted to that use (please see the argumentation advanced above against e.g. for D7).

The reference discloses at column 14 as example B 14 an example demonstrating activity against *Lucilia cuprina*. The test method described is a typical in-vitro test demonstrating insect-development inhibiting activity. For this purpose eggs of the parasite are treated with a nutrient containing active compound. This test does not give any indication about the most advantageous method of application to combat parasites such as fleas on animals.

The reference discloses at column 15 as example B 15 an example allegedly demonstrating activity against *Ctenocephalides felis*. The test method described is also a typical in-vitro test demonstrating insect development inhibiting activity. The test does not allow any conclusion to the treatment of the host-animal. Flea

eggs fall off the animal and are hatched in the surroundings of the animal. If at all this test method indicates that fleas should be combated by treating the flea eggs in the surrounding of host animals. The test description does not give the slightest indication how host animals should be treated advantageously to free them longlastingly from parasites such as fleas.

16. EP-A 183-855 (NBA) (Reference D16)

This reference discloses new insecticidally active compounds at page 5, line 30 to page 7, and the reference makes general remarks about the application of these compounds in the fields of plant protection, stored goods and hygienics. At page 8, lines 1-12, it is mentioned that compounds may be used in the field of veterinary medicine against noxious animal parasites such as insects and worms. The reference is silent about the treatment method. As in reference D5 reference D16 does not distinguish between systemic and non-systemic treatment methods. Endo-parasites such as worms have to be treated by a method which brings the active compound into the body of the host-animal. These are oral, parenteral or trans-dermal application methods. From D4 it was known that these would be advantageous treatment methods also in the case of treatment against ecto-parasites.

In principle ecto-parasites could also be combated by non-systemic, dermal, treatment. But as it is worked out in D4 this treatment method is disadvantageous. The present invention which is concentrating on this non-systemic dermal treatment method which has been disregarded by prior art (D4) could not be anticipated or made obvious by a reference which is silent about the selection of suitable treatment or application methods.

17. DE-A 4 207 604 (Ciba) (Reference D17)

The reference discloses new insecticidally active compounds. On page 3, lines 29-32, all possible application fields such as agriculture, forestry, protection of stored goods and hygienic field are listed. (The English translation given in the opposition paper for line 32 is not correct. The respective part of the sentence in German language reads:

... im Hygienesektor insbesondere an Haus- und Nutztieren vorkommen.

The translation given reads:

... in the hygiene sector, and especially for the protection of domestic animals and productive livestock.

The correct translation would read:

... in the hygiene sector especially for the protection of domestic animals and productive livestock.

For unknown reasons D17 counts animal treatment to the hygiene field. By no means is their treatment especially emphasized in D17.)

The reference gives a nearly complete list of pests. Most of them are relevant in agriculture, forestry and protection of stored goods. The reference does not distinguish the insect pests relevant for animal health or human health nor does it indicate suitable application methods. Therefore also for this reference the argumentation advanced above against D7 and D8 (above) applies.

18. EP-A 375 907 (NBA) (Reference D18)

The reference discloses new insecticidally active compounds. As in the case of reference D16 also D18 makes general remarks that the new compounds can be used in the field of veterinary medicine. But also D18 leaves it to the evaluation of the reader how to apply these new compounds in the most successful way to

animals and humans. Therefore also here a person skilled in the art has to rely on his knowledge and on prior art such as D4. A person skilled in the art would, in view of D4, not have considered the present inventive method as an advantageous possibility. Therefore the reference neither anticipates the present invention nor makes it obvious.

19. EP-A 296 453 (NBA) (Reference D19)

The reference describes new insecticidally active compounds. As in the case of references D16 and D18 reference D19 does not teach anything beyond the general remark that the compounds can be used in veterinary medicine. The reference is absolutely silent about application methods and specifically about the advantageous non-systemic dermal application method according to the present invention.

20. EP-A 259 738 (NBA) (Reference D20)

The reference describes new insecticidally active compounds. As in the case of references D16, D18 and D19 reference D20 does not teach anything beyond the general remark that the compounds can be used in veterinary medicine. The reference is absolutely silent about application methods and specifically about the advantageous non-systemic dermal application method according to the present

invention.

21. EP-A 386 565 (NBA) (Reference D21)

The reference discloses new insecticidally active compounds. At page 5, line 17, through page 6, line 3, pests which could be combated with the active compounds are listed. This list does not distinguish between uses in agriculture, forestry, protection of stored goods and hygiene. Nowhere in D21 is the specific non-systemic dermal application method which is an essential and advantageous part of the present invention mentioned. Therefore also here the argumentation advanced above against D16 applies.

22. EP-A 315 826 (NBA) (Reference D22)

Also the reference describes new insecticidally active compounds. As in reference D21 the reference D22 discloses on page 6, line 35 to page 7, line 34 a list of insects against which the compounds can be used. The reference is silent about application methods suitable in the animal health field. The reference is especially silent about the specific non-systemic dermal application method which is part of the present invention. Therefore, the same argumentation applies as for D16.

23. EP-A 383 091 (NBA) (Reference D23)

The reference discloses new insecticidally active compounds. As in the case of reference D16 reference D23 does not teach anything beyond the general remark that the compounds can be used in veterinary medicine. The reference is absolutely silent about application methods and specifically about the advantageous non-systemic dermal application method according to the present invention. Therefore the same argumentation as for D16 also applies for reference D23.

24. GB-A 2 228 003 (Reference D24)

The reference describes new insecticidally active compounds. The reference does not given any indication that these compounds can be used in the fields of animal health or human health to combat parasites. Nor does the reference disclose any application method specific for these use-fields. The reference simply says at page 7, last line, to page 8, first line, that the compounds are used by "... treating the locus with a pesticidal compound or composition ... ". Nothing is said about the treatment method itself. The reference does therefore neither anticipate nor make obvious the present invention.

25. EP-A 254 859 (NBA) (Reference D25)

The reference discloses new insecticidally active compounds. As in the case of reference D16 reference D25 does not teach anything beyond the general remark that the compounds can be used in veterinary medicine. The reference is absolutely silent about application methods and specifically about the advantageous non-systemic dermal application method according to the present invention. Therefore the same argumentation as for D16 also applies for reference D25.

26. GB-A 2 271 110 (corresponds to EP-A 583 198 or DE-A 4 326 983)
(Reference D26)

Reference D26 discloses new insecticidally and acaricidally active compounds. Also in this reference all possible uses for insecticides or acaricides are listed. The reference characterizes insects or acarids as parasites independently from their occurrence. Usually only insects or acarids damaging animals or humans are characterized as parasites. Therefore the broad use of the expression parasiticide in reference D26 is no indication for special importance of the use in the animal health field.

The reference emphasizes the particular suitability of the active compounds against ticks and mites. The present invention is not directed against these pests which belong to a totally different order of arthropods than insects. The present invention is only concerned with an application method against insects. At page 4, lines 2-4, (DE-A 4 326 983) the reference emphasizes that the compounds are used to combat diseases caused by ticks and mites on animals and humans. (By the way, through a translation error in the German text at page 4, line 5 use against "lice" is mentioned. The correct translation would have been "mites" in this place.) At page 4, lines 7-10 as application methods vaporizing, shampooing, bathing or painting-on is mentioned as well as the pour-on method. All this is mentioned in combination with treatment of animals and humans against ticks and mites (scabies). This reference is close to the present invention, but it does not disclose the particular suitability of the non-systemic dermal use against parasitic insects on animals and especially against fleas. In particular it does not disclose the extended term of protection dermal treatment gives against insect parasites on animals.

27. EP-A 285 985 (Bayer) (Reference D27)

This reference discloses new insecticidally active compounds. On page 7, lines 24-38 the reference discloses that the compounds may be used to combat arthropods on animals. The reference lists all possible application methods such as

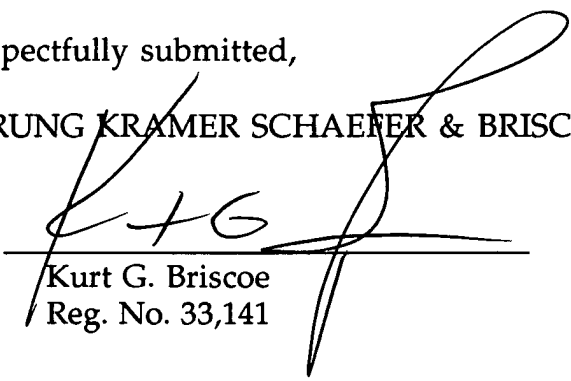
oral or enteral or parenteral methods which would be considered as systemic methods. The reference also lists dermal methods. But the reference makes no distinction between enteral or parenteral and dermal methods. All seem to be equally suitable. Reference D4 made clear that the dermal treatment method had drastic disadvantages and therefore would not be considered by those skilled in the art as an advantageous application method. Example E on page 15, lines 33-43, is a typical in-vitro test. The test demonstrates that the compounds are active against *lucilia cuprina*. The test discloses nothing about any particular application method in the animal health field against this fly. Therefore also reference D27 in the light reference D4 neither anticipates nor makes obvious the present invention.

Consideration of the foregoing in connection with this application is respectfully requested.

Respectfully submitted,

SPRUNG KRAMER SCHAEFER & BRISCOE

By


Kurt G. Briscoe
Reg. No. 33,141

660 White Plains Road
Fourth Floor
Tarrytown, New York 10591-5144
(914) 332-1700